Diagnostic Value of HepPar1, pCEA, CD10, and CD34 Expression in Separating Hepatocellular Carcinoma From Metastatic Carcinoma in Fine-Needle Aspiration Cytology

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Differentiating primary and metastatic hepatic malignancies can be diagnostically challenging in fine-needle aspiration cytology (FNAC). We compared four immunohistochemical (IHC) markers, pCEA, CD10, HepPar1, and CD34, in differentiating hepatocellular carcinoma (HCC) from metastatic carcinoma (MC) in FNAC specimens. Sixty cases of liver FNAC with their corresponding cell blocks were retrieved from the hospital computer system, including 30 HCC and 30 MC (15 colon, 10 breast, and 5 pancreas). The diagnoses were confirmed by clinical follow-up and surgical resection or core needle biopsy. The direct cytologic smears were air-dried and Diff-Quik-stained, and alcohol-fixed and Papanicolaou-stained. Cell block sections from the aspirates were immunostained for pCEA, CD10, HepPar1, and CD34. IHC on cytologic smears for HCC was performed on 10 cases and compared with the cell block results. In HCC, CD10, and pCEA demonstrated the characteristic canalicular staining in 23/30 (77%) and 24/30 (80%) of the cases, respectively; however, none of the MC showed a canalicular staining pattern. HepPar1 was positive in 26/30 (87%) of the HCC cases and one MC. CD34 stained sinusoidal endothelial cells in 27/30 (90%) cases of HCC and six MC. Our results demonstrate that the canalicular staining pattern for CD10 and sinusoidal staining pattern of CD34 are very specific, in addition to the high specificity and sensitivity of HepPar1 for HCC. Cell blocks were more informative in demonstrating the characteristic architecture and immunostaining pattern of the malignancy than the cytologic smears. An IHC panel consisting of pCEA, CD10, HepPar1, and CD34 is useful for confirming HCC in FNAC of the liver. Diagn. Cytopathol. 2004;30:1–6.

Key Words: FNA; hepatocellular carcinoma; CD10; HepPar1; immunohistochemistry

Although hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy in adults, metastatic neoplasms constitute the majority of hepatic cancer.[1] With advancements in current imaging techniques, fine-needle aspiration cytology (FNAC) of hepatic lesions has become more popular and an accurate diagnosis can often be rendered. However, application of immunohistochemistry (IHC) can often be helpful in the separation of primary and metastatic malignancies of the liver, since a variety of histologic patterns and overlapping morphologic features can be seen in HCC and metastatic malignancies.[2–6] Moreover, the treatment and prognosis of HCC and metastatic carcinoma (MC) are significantly different and the ability to distinguish primary from metastatic malignancy is clinically important.[7]

Many markers have been suggested to differentiate HCC from MC with various specificities and sensitivities. Alpha-fetoprotein (AFP), a commonly used marker for HCC differentiation, is relatively specific for HCC, but has a low sensitivity, ranging from 17–71%.[8–11] Recently, hepatocyte paraffin-1 (HepPar1) has been reported to be a highly specific marker for hepatocytic differentiation with a very high sensitivity, approaching 90%.[7,8] Neprilysin (CD10) and polyclonal antibody against carcinoembryonic antigen (pCEA) can help distinguish HCC from MC, based on the

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Table I. Characteristics of antibodies used in the study

Antibody	*Clone*	*Pretreatment*	*Dilution*	*Ab. incubation*	*Localization*	*Source*
PCEA	Polyclonal	None	1:400	32 min/40°C	Canalicular	Dako
CD10	56c6	Steamer*	Neat	32 min/40°C	Canalicular	Ventana
HepPar1	OCH1E5	Steamer*	1:50	1 hr/RT	Cytoplasmic	Dako
CD34	QBend-10	Steamer*	Neat	32 min/40°C	Sinsoids	Ventana

RT = room temperature; memb. = membrane; Ab. = antibody; Neat = without dilution.
*In citrate buffer.

characteristic canalicular staining pattern of HCC and the diffuse cytoplasmic staining pattern of some MC.[12–15] Benign hepatic sinusoids are different from other small blood vessels, since they do not express endothelial cell markers such as *Ulex europaeus* binding, von-Willebrand factor (vWF), or CD34.[16,17] In HCC, however, the sinusoidal cells undergo a process of "capillarization," where they show loss of the fenestrae, deposition of basement membrane, and express diffuse staining for CD34.[18] This feature has been reported as useful in distinguishing benign from malignant primary hepatocytic neoplasms in cytologic specimens.[19]

In this study, we compare the sensitivity and specificity of the immunohistochemical (IHC) markers pCEA, CD10, HepPar1, and CD34 in differentiating HCC from MC in FNAC specimens.

Materials and Methods

Case Selection

FNAC of 30 cases of HCC and 30 cases of metastatic malignancies to the liver with adequate cell-block material were retrieved from the archives of the Allegheny General Hospital during the period between January 1998 and July 2002. The study was approved by the Institutional Review Board. All FNA biopsies were performed using radiologic guidance. A cytopathologist was present at the FNA procedure to assess the adequacy of the sample, give a preliminary diagnosis, and prepare the aspirated material. Cell blocks were fixed in Hank's solution and paraffin-embedded. The cytologic smears were divided into two parts: air-dried, Diff-Quik-stained and alcohol-fixed, Papanicolaou-stained smears. Two hematoxylin and eosin (H&E)-stained sections from cell blocks were prepared and evaluated to assure adequacy for IHC studies. Thin core biopsies were performed on 25 patients (15 HCC and 10 MC) at the time of the FNA using an 18-gauge needle and were fixed in formalin, paraffin-embedded, and stained with H&E. The original diagnosis was confirmed on the basis of clinical follow-up including serum α-fetoprotein, imaging findings, and tumor resection in 20 cases or core needle biopsies in 25 cases. IHC was formed on 10 alcohol-fixed cytologic smears of HCC for comparison with the cell block results.

Antibodies

Table I details the characteristics, pretreatments, dilutions, incubation periods, localizations, and sources of the four antibodies used in the study.

Immunohistochemistry

Multiple 4-μm-thick sections from the paraffin-embedded cell blocks were used for IHC studies. The sections were mounted on coated slides and dried for 1 hr at 60°C. For IHC studies, the sections were deparaffinized in xylene and rehydrated in a descending ethanol series. Antigen expression was enhanced by heat treatment of sections in a steamer with citrate buffer for CD10, HepPar1, and CD34. Pretreatment was not done for pCEA and the IHC studies performed on the alcohol-fixed cytology smears.

After preincubation with 1% bovine serum albumin (Sigma, St. Louis, MO)/TBS for 5 min, the primary antibodies were applied at appropriate dilutions for time periods and temperatures as indicated in Table I. After washing in TBS, the slides were subsequently processed by the Ventana (Tucson, AZ) autostainer.

Microscopic Evaluation

Three observers (RSS, TML, YL) blindly assessed the immunostaining without knowledge of the previous clinical, radiologic, or histopathologic diagnoses and the staining was recorded as positive or negative. The distribution pattern of reactivity for pCEA and CD10 was recorded as canalicular, membranous, and/or cytoplasmic. Only canalicular staining for pCEA and CD10 was considered specific for HCC. For HepPar1, positivity was defined as an unequivocally positive coarsely granular cytoplasmic staining that could not be confused with background staining or endogenous peroxidase staining. CD34 staining of the endothelial cells rimming the tumor cell groups in HCC was considered positive and indicative of hepatocytic differentiation. After the cases were evaluated the diagnoses were revealed and staining patterns of the various tumors compared. Statistical analysis was performed to determine the sensitivity and specificity of each IHC marker for differentiating HCC from MC.

Table II. Immunohistochemical data and statistics

	HCC (30 cases)		MC (30 cases)				
	No.	*%*	*No.*	*%*	*Sensitivity*	*Specificity*	*PPV*
PCEAcan	24	80%	0	0%	80%	100%	100%
CD10can	23	77%	0	0%	77%	100%	100%
HepPar1	26	87%	1	4%	87%	97%	96%
CD34	27	90%	6	20%	90%	80%	82%

pCEAcan = canalicular staining pattern with pCEA; CD10can = canalicular staining pattern with CD10.

Results

The FNC diagnosis was confirmed by clinical follow-up data, including AFP and radiographic imaging, with tumor resection in 20 cases or core needle biopsy in 25 cases. Table II details the results, including sensitivity, specificity, and positive predictive values of the different immunohistochemical stains.

pCEA and CD10

Of the 30 cases of HCC, a canalicular pattern was demonstrated in 23/30 (77%) with CD10 and 24/30 (80%) using pCEA. The canalicular stains in well-differentiated HCC showed a long branching and zigzag linear pattern, whereas in poorly differentiated HCC the stain was a thick, short line or sometimes dot-like (Fig. C-1A,B). Membranous staining was demonstrated in 9/30 (30%) with CD10 and 13/30 (43%) using pCEA, while cytoplasmic staining was seen in 6/30 (20%) with CD10 and 16/30 (53%) with pCEA. No canalicular immunostaining pattern was detected in any case of MC for either CD10 or pCEA. Three cases of HCC showed very strong membranous staining for pCEA, which compromised the evaluation (Fig. C-2A). In these three cases, CD10 was helpful in confirming a canalicular staining pattern (Fig. C-2B). One HCC case was negative for pCEA, but positive for CD10 (Fig. C-3A,B). In MC, membranous and cytoplasmic immunostaining was detected in 9/30 (30%) and 12/30 (40%) with CD10, and 17/30 (57%) and 27/30 (90%) with pCEA, respectively. The sensitivity and specificity were 77% and 100% for CD10 and 80% and 100% for pCEA, respectively, for HCC.

HepPar1

Using the HepPar1 antibody, 26/30 (87%) of HCC exhibited immunoreactivity in at least 10% of tumor cells (Fig. C-4A,B). Poorly differentiated HCC demonstrated less staining than well-differentiated HCC. Benign-appearing hepatocytes demonstrated uniform HepPar1 expression and were helpful as an internal positive control. In comparison, 29/30 (96%) of MC exhibited no immunoreactivity with HepPar1. Only one case (4%) of metastatic colon cancer showed focal immunoreactivity with HepPar1, staining less than 10% of malignant cells. Therefore, the sensitivity of HepPar1 for HCC was 87%, and specificity was 97%.

CD34

For CD34, 27/30 of HCC (90%) showed diffuse endothelial staining, while 21/30 (70%) demonstrated the characteristic diffuse staining pattern of endothelial cells rimming around the tumor cell aggregates, in both the cell blocks and core biopsies (Fig. C-5A,B). In normal liver tissue, CD34 was negative or only focally positive. Therefore, only diffuse CD34 staining was considered a positive. The grade of HCC did not appear to correlate with the CD34 score. CD34 stained three cases of poorly differentiated HCC, which were negative for CD10 and pCEA (two cases) and for HepPar1 (one case). In MC, diffuse endothelial CD34 staining was identified in 6/30 (20%) cases. However, these cases showed diffuse staining of endothelial cells in tumor tissue, without showing the characteristic rimming pattern around the tumor cell aggregates. The sensitivity and specificity of diffuse CD34 staining for HCC was 90% and 80%, respectively. The positive predictive value of CD34 for HCC was 82%.

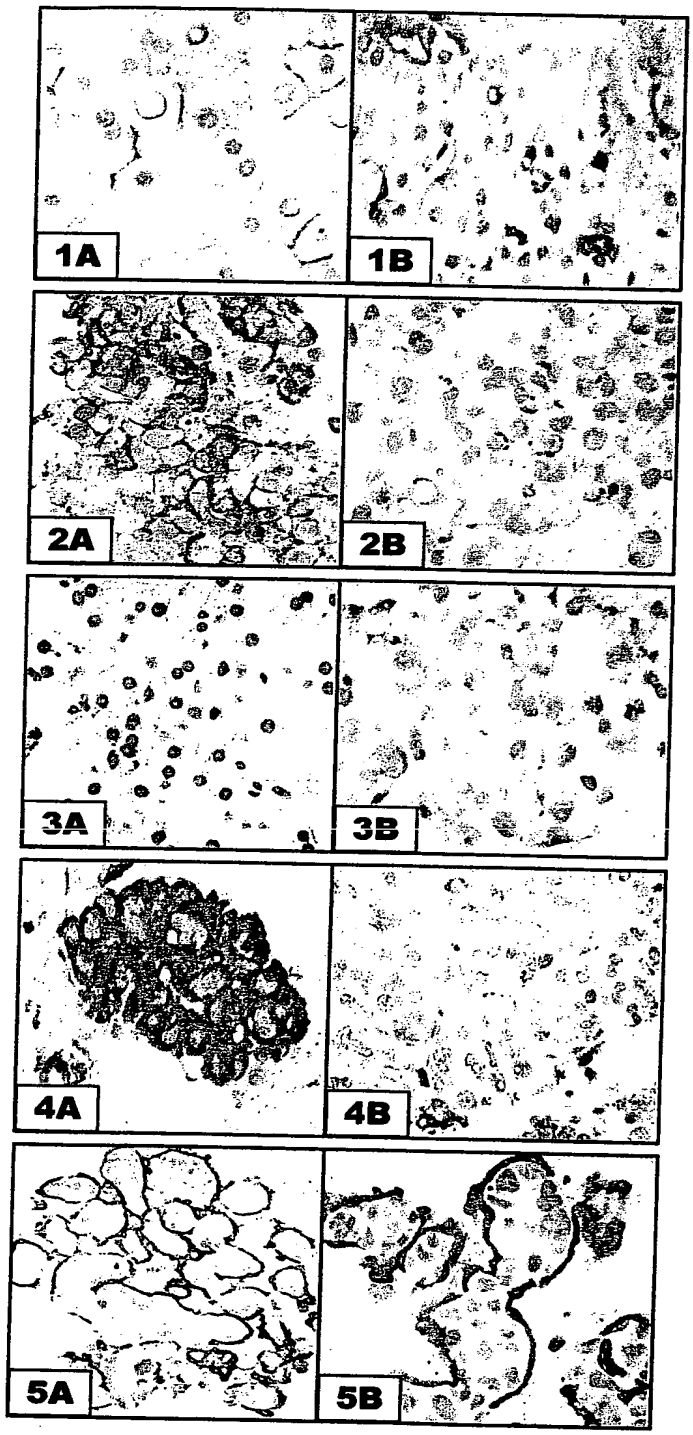
In cytology smears, we examined the staining pattern of all four antibodies performed on 10 smears. The canalicular pattern was difficult to interpret, but careful searching identified canalicular staining in 5/10 with CD10 and 6/10 with pCEA. We found that HepPar1 and CD34 staining to be much easier to interpret in smears, with 9 of 10 smears of HCC cases staining positively with HepPar1 and 8 of 10 with CD34.

Discussion

Distinguishing HCC from MC in FNAC of liver lesions can occasionally be a diagnostic challenge. In this study we compared the sensitivity and specificity of four available IHC markers, pCEA, CD10, HepPar1, and CD34, in distinguishing HCC from MC in FNAC specimens. We retrieved 60 cases (30 HCC and 30 MC) with diagnostic material on the cell blocks along with clinical and/or histologic confirmation.

pCEA is a polyclonal antibody that cross-reacts with the biliary glycoprotein 1 along the bile canalicular space.[20] In our study, pCEA stained 24/30 (80%) cases of HCC with a canalicular pattern. Membranous and cytoplasmic staining was also seen in HCC, but was not specific, since 12/30 (57%) and 27/30 (90%) cases of MC also demonstrated a cytoplasmic/membranous staining pattern, respectively. Therefore, a canalicular staining pattern of immunoreactivity was highly indicative of HCC because this pattern was not identified in any of the MC. Previous investigations have reported a canalicular staining pattern for pCEA in 24–90% of HCC cases, which is dependent on the number of poorly differentiated HCC cases included in the studies, since canalicular staining is less common in poorly differentiated HCC.[12,20–24]

CD10, a 100-kd cell surface glycoprotein, is a type II integral membrane protein known as neutral endopepti-



Figures C-1–C-5.

dase,[25,26] which participates in the postsecretory processing of neuropeptides and peptide hormones. CD10 was originally identified on cells of acute lymphoblastic leukemia, and thus named common acute lymphoblastic leukemia antigen (CALLA).[26] Recent studies showed that CD10 is also expressed by a variety of nonhematopoietic neoplasms such as carcinomas of the liver, pancreas, kidney, bladder, prostate, and uterus.[15,27,28]

Chu et al.[23] first noted that CD10 stained normal liver tissue and HCC in a canalicular pattern similar to that of pCEA. Our study showed that, although the specificity is 100%, the sensitivity of CD10 in HCC is only about 77%, which is similar to that of pCEA (80%). In our series, both HCC and MC also expressed CD10 in the cytoplasm and/or cell membrane, but to a lesser degree than pCEA. However, only nonneoplastic liver tissue and HCCs showed the characteristic canalicular staining pattern, which is similar to the one observed with pCEA. In our study, the canalicular staining in well-differentiated HCC showed a long branching and zigzag linear pattern, whereas in poorly differentiated HCC the staining was either thick, short line, or sometimes dot-like. It has been suggested that CD10 is a more specific marker, since it specifically stains bile duct glycoprotein but does not react with other antigens in the CEA family.[22]

The characteristic canalicular staining of pCEA and CD10 has been regarded as the most useful of all positive findings in distinguishing HCC from MC. However, in some cases the pCEA canalicular staining pattern may be difficult to interpret. In the current study we found membranous staining for CD10 and pCEA in 30% and 43% of HCC, respectively. When the membrane staining is very strong, it can mask canalicular staining. In our study, three cases of HCC showed strong membranous staining for pCEA, which compromised the evaluation for canalicular staining. However, CD10 was helpful in these cases in confirming the canalicular pattern of staining since there was no cytoplasmic/membranous staining present. Also, incomplete membranous staining of MC may mimic the canalicular staining seen in HCC. However, none of our MC cases showed this incomplete membranous pattern, al-

Fig. C-1. A: Well-differentiated HCC showing the branching canalicular staining pattern for CD10. **B:** Poorly differentiated HCC with short line or dot-like canalicular staining pattern with CD10. (IHC, **A:** ×400; **B:** ×250.)
Fig. C-2. A: Strong membranous staining pattern of HCC with pCEA can be difficult to interpret. **B:** However, CD10 showed the characteristic canalicular staining for the same case. (IHC, ×400.)
Fig. C-3. A,B: HCC negative for pCEA and positive for CD10 with the characteristic canalicular staining pattern (IHC, ×400).
Fig. C-4. A,B: HCC with strong granular cytoplasmic immunoreactivity with HepPar1 (IHC, ×400).
Fig. C-5. A,B: Two different cases of HCC showed the characteristic strong diffuse of sinusoidal endothelial rimming staining pattern for CD34. This feature is important to differentiate HCC from benign hepatic lesion and metastatic carcinoma. (IHC, **A:** x250; **B:** ×400.)

though it has been reported for pCEA.[14] In contrast, membranous staining of MC and HCC with CD10 is less common and less intense. Therefore, CD10 can be helpful in cases with equivocal canalicular-membranous staining with pCEA and in cases with negative staining.[23]

In 1993, Wennerberg et al.[30] developed a new monoclonal antibody called hepatocyte paraffin-1 (HepParl). These investigators injected mice with tissue from failed liver allograft to develop a single clone (OCH1E5.2.10) isolated from myeloma hybridomas that can recognize mitochondrial antigen of hepatocytes,[30,31] HepParl reacts with both normal and neoplastic hepatocytes in routine formalin-fixed, paraffin-embedded material, producing distinct granular cytoplasmic staining of hepatocytes.

In our study, HepParl exhibited comparable sensitivity to pCEA and CD10 for staining HCC. The previously reported sensitivity of HepParl in classic HCC is 90%,[30–33] which is similar to our results (87%). In one study, poorly differentiated HCC and HCC with a compact growth pattern showed immunoreactivity in more than 80% of cases for HepParl, which is comparable with the upper limit of sensitivity of pCEA and higher than that of AFP.[8,11] Our study showed that HepParl did not stain most metastases from the colon, breast, or pancreatic sites (with one exception). Also, a recent study showed that HepParl did not stain metastatic squamous cell, neuroendocrine, or transitional cell carcinoma.[23] However, HepParl can occasionally stain the cytoplasm of MC involving the liver.[34,35] Both primary gastric and esophageal adenocarcinomas and their metastatic lesions to the liver can demonstrate HepParl reactivity in a high percentage (70–75%).[35,36] Recently, HepParl immunoreactivity was also detected in urinary bladder, pulmonary, colonic, adrenal cortical, yolk sac tumor, ovarian, and endocervical adenocarcinomas.[36,37] Therefore, this finding may potentially have diagnostic implications, since the demonstration of HepParl reactivity in cell blocks from an FNAC of a hepatic neoplasm should not be unequivocally considered evidence of HCC, but rather should be evaluated in the appropriate clinical setting.[35]

There have been several histologic studies examining the utility of vascular markers (especially CD34) in making a distinction between benign hepatic lesions and HCC. These studies found that HCC showed diffuse positivity for CD34 in sinusoidal vessels, while sinusoids in benign lesions were negative.[38–42] This process of sinusoidal capillarization has been reported in most HCC.[43,44] However, some HCC did not stain with CD34, while other benign or dysplastic lesions showed periportal and periseptal staining.[16,42] Therefore, in FNAC, positive staining can be seen in some benign lesions, particularly if the sample contains periportal and periseptal tissue. There have been few previous FNA studies of CD34 staining of liver lesions using cell block material.[19,42,43] These studies showed that HCC showed more diffuse and stronger staining than benign lesions and concluded that CD34 staining can aid in distinguishing HCC from benign hepatic lesions in FNAC of the liver. Our study showed that strong and diffuse CD34 staining in either cell block or core biopsy supports a diagnosis of HCC. However, positive staining is not specific, since six cases of MC also showed diffuse staining. However, endothelial rimming staining around the border of tumor aggregates, seen in 70% of HCC, was very specific, since it was not seen in MC.

All four IHC markers evaluated in our study are prone to sampling variations. An HCC having moderately and poorly differentiated areas may give IHC results that vary, depending on the area sampled. Thus, to reduce sampling variation one should consider using a panel of IHC markers. By comparing the staining patterns of pCEA, CD10, HepParl, and CD34, we were able to show that no HCC was negative for all four IHC markers. A combination of pCEA, CD10, HepParl, and CD34 was diagnostic in 100% of HCC.

In conclusion, we recommend an IHC panel of HepParl, pCEA, CD10, and CD34 be utilized for the diagnosis of HCC to increase diagnostic accuracy. Accordingly, it is important to obtain a cell block or core biopsy on all FNA cases in which the preliminary interpretation raises the possibility of a differential diagnosis of HCC vs. MC. In cases in which a cell block is not available, markers such as HepParl and CD34 can still be done on cytology smears.

References

1. Di Bisceglie AM, Carithers RL Jr, Gores GJ. Hepatocellular carcinoma. Hepatology 1998;28:1161–1165.
2. Pisharodi LR, Lavoie R, Bedrossian CW. Differential diagnostic dilemmas in malignant fine-needle aspirates of liver: a practical approach to final diagnosis. Diagn Cytopathol 1995;12:364–370.
3. Zimmerman RL, Burke M, Young NA, Solomides CC, Bibbo M. Diagnostic utility of Glut-1 and CA 15-3 in discriminating adenocarcinoma from hepatocellular carcinoma in liver tumors biopsied by fine-needle aspiration. Cancer Cytopathol 2002;96:53–57.
4. Ishikura H, Kishimoto T, Andachi H, Kakuta Y, Yoshiki T. Gastrointestinal hepatoid adenocarcinoma: venous permeation and mimicry of hepatocellular carcinoma, a report of four cases. Histopathology 1997;31:47–54.
5. Serrano R, Rodriguez-Peralto JL, Santos-Briz A, de Agustin P. Fine needle aspiration cytology of metastatic hepatic adrenocortical carcinoma mimicking hepatocellular carcinoma: a case report. Acta Cytol 2000;45:768–770.
6. Maitra A, Murakata LA, Albores-Saavedra A. Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinomas of the gastrointestinal tract. Am J Clin Pathol 2001;115:689–694.
7. Zimmerman R, Burke MA, Young NA, Solomides CC, Bibbo M. Diagnostic value of hepatocyte paraffin 1 antibody to discriminate hepatocellular carcinoma from metastatic carcinoma in fine needle aspiration biopsies of the liver. Cancer Cytopathol 2001;93:288–291.
8. Minervini MI, Demetris AJ, Lee RG, Carr BI, Madariaga JM, Nalesnik MA. Utilization of hepatocyte-specific antibody in the immunocytochemical evaluation of liver tumors. Mod Pathol 1997;10:686–692.
9. D'Errico A, Baccarini P, Fiorentino M, et al. Histogenesis of primary liver carcinomas: strengths and weaknesses of cytokeratin profile and albumin mRNA detection. Hum Pathol 1996;27:599–604.
10. Hurlimann J, Gardiol D. Immunohistochemistry in the differential diagnosis of liver carcinomas. Am J Surg Pathol 1991;15:280–288.

11. Ma CK, Zarbo RJ, Frierson HF Jr, Lee MW. Comparative immunohistochemical study of primary and metastatic carcinomas of the liver. Am J Clin Pathol 1993;99:551–557.
12. Christensen WN, Boitnott JK, Kuhajda FP. Immunoperoxidase staining as a diagnostic aid for hepatocellular carcinoma. Mod Pathol 1989;2:8–12.
13. Dragovic T, Deddish PA, Tan F, Weber G, Erdos EG. Increased expression of neprilysin (neutral endopeptidase 24.11) in rat and human hepatocellular carcinoma. Lab Invest 1994;70:107–113.
14. Dragovic T, Sekosan M, Becker RP, Erdos EG. Detection of neutral endopeptidase 24.11 (neprilysin) in human hepatocellular carcinomas by immunocytochemistry. Anticancer Res 1997;17:3233–3238.
15. Loke SL, Leung CY, Chiu KY, Yan WL, Cheung N, Ma L. Localization of CD10 to biliary canaliculi by immunoelectron microscopical examination. J Clin Pathol 1990;43:654–656.
16. Park YN, Yang CP, Fernandez GJ, Cubukcu O, Thung SN, Theise ND. Neoangiogenesis and sinusoidal "capillarization" in dysplastic nodules in the liver. Am J Surg Pathol 1998;22:656–662.
17. Dhillon A, Colombari R, Savage K, Scheuer P. An immunohistochemical study of the blood vessels within primary hepatocellular tumors. Liver 1992;12:311–318.
18. Ohmori S, Shiraki K, Sugimoto K, et al. High expression of CD34 positive sinusoidal endothelial cells is a risk factor for hepatocellular carcinoma in patients with HCV-associated chronic liver disease. Hum Pathol 2001;32:1363–1370.
19. Abraham S, Sack M, Furth EE. The utility of CD34 in distinguishing hepatocellular carcinoma from non-neoplastic lesions in fine needle aspirates of the liver. Mod Pathol 1999;12:39A.
20. Wong MA, Yazdi HM. Hepatocellular carcinoma versus carcinoma metastatic to the liver. Value of stains for carcinoembryonic antigen and napthylamidase in fine needle aspiration biopsy material. Acta Cytol 1990;34:192–196.
21. Morrison C, Marsh W, Frankel WL. A comparison of CD10 to pCEA, MOC31, and hepatocyte for the distinction of malignant tumors in the liver. Mod Pathol 2002;15:1279–1287.
22. Borscheri N, Roessber A, Rocken C. Canalicular immunostaining of Neprilysin (CD10) as a diagnostic marker for hepatocellular carcinomas. Am J Surg Pathol 2001;25:1297–1303.
23. Chu PG, Ishizawa S, Wu E, Weiss LM. Hepatocyte antigen as a marker of hepatocellular carcinoma: an immunohistochemical comparison to carcinoembryonic antigen, CD10 and alpha-fetoprotein. Am J Surg Pathol 2002;26:978–988.
24. Ishak KG, Goodman ZD, Stocker JT. Hepatocellular carcinoma. In: Ishak KG, Goodman ZD, Stocker JT, editors. Atlas of tumor pathology: tumor of the liver and intrahepatic bile ducts. Washington, DC: Armed Forces Institute of Pathology; 2001. p 199–244.
25. Ritz J, Pesando JM, Notis-McConarty J, Lazarus H, Schlossman SF. A monoclonal antibody to human acute lymphoblastic leukaemia antigen. Nature 1980;283:583–585.
26. Shipp MA, Vijayaraghavan J, Schmidt EV, et al. Common acute lymphoblastic leukemia antigen (CALLA) is active neutral endopeptidase 24,11 ("enkephalinase"): direct evidence by cDNA transfection analysis. Proc Natl Acad Sci USA 1989;86:297–301.
27. McIntosh GG, Lodge AJ, Watson P, et al. NCL-CD10-270: a new monoclonal antibody recognizing CD10 in paraffin-embedded tissue. Am J Pathol 1999;154:77–82.
28. Chu P, Arber DA. Paraffin-section detection of CD10 in 505 nonhematopoietic neoplasms: frequent expression in renal cell carcinoma and endometrial stromal sarcoma. Am J Clin Pathol 2000;113:374–382.
29. Xiao SY, Wang HL, Hart J, Fleming D, Beard MR. cDNA arrays and immunohistochemistry identification of CD10/CALLA expression in hepatocellular carcinoma. Am J Surg Pathol 2001;159:1415–1421.
30. Wennerberg AE, Nalesnik MA, Coleman WB. Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 1993;143:1050–1054.
31. Siddiqui MT, Saboorian MH, Gokaslan ST, Ashfaq R. Diagnostic utility of the HepPar1 antibody to differentiate hepatocellular carcinoma from metastatic carcinoma in fine-needle aspiration samples. Cancer Cytopathol 2002;96:49–52.
32. Leong AS, Sormunen RT, Tsui WM, Liew CT. HepPar1 and selected antibodies in the immunohistological distinction of hepatocellular carcinoma from cholangiocarcinoma, combined tumors and metastatic carcinoma. Histopathology 1998;33:318–324.
33. Murakata LA, Ishak KG, Nzeako UC. Clear cell carcinoma of the liver: a comparative immunohistochemical study with renal clear cell carcinoma. Mod Pathol 2000;13:974–881.
34. Terracciano LM, Glatz K, Mhawech P, et al. Hepatoid adenocarcinoma with liver metastasis mimicking hepatocellular carcinoma: An immunohistochemical and molecular study of eight cases. Am J Surg Pathol 2003;27:1302–1312.
35. Maitra A, Murakata LA, Albores-Saavedra J. Immunoreactivity for hepatocyte paraffin 1 antibody in hepatoid adenocarcinoma of the gastrointestinal tract. Am J Clin Pathol 2001;115:689–694.
36. Kakar S, Muir T, Murphy LM, Lloyd RV, Burgart LJ. Immunoreactivity of Hep Par1 in hepatic and extrahepatic tumors and its correlation with albumin in situ hybridization in hepatocellular carcinoma. Am J Clin Pathol 2003;119:361–366.
37. Fan Z, van de Rijn M, Montgomery K, Rouse RV. Hep Par1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 2003;16:137–144.
38. Dhillon AP, Colombari R, Savage K, Scheuer PJ. An immunohistochemical study of the blood vessels within primary hepatocellular tumor. Liver 1992;12:311–318.
39. Ruck P, Ziao JC, Kaiserling E. Immunoreactivity in sinusoids in hepatocellular carcinoma: An immunohistochemical study using lectin UEA-1 and antibodies against endothelial markers, including CD34. Arch Pathol Lab Med 1995;119:173–178.
40. Cui S, Hano H, Sakata A, et al. Enhanced CD34 expression of sinusoid-like vascular endothelial cells in hepatocellular carcinoma. Pathol Int 1996;46:751–756.
41. Maeda T, Adachi E, Kajiyama K, et al. CD34 expression in endothelial cells of small hepatocellular carcinoma: its correlation with tumor progression and angiographic findings. J Gastroenterol Hepatol 1995; 10:650–654.
42. de Boer WB, Segal A, Frost FA, Sterrett GF. Can CD34 discriminate between benign and malignant hepatocytic lesions in fine needle aspirates and thin core biopsies? Cancer Cytopathol 2000;90:273–278.
43. Gottschalk-Sabag S, Ron N, Glick T. Use of CD34 and factor VIII to diagnose hepatocellular carcinoma on fine needle aspirates. Acta Cytol 1998;42:691–696.